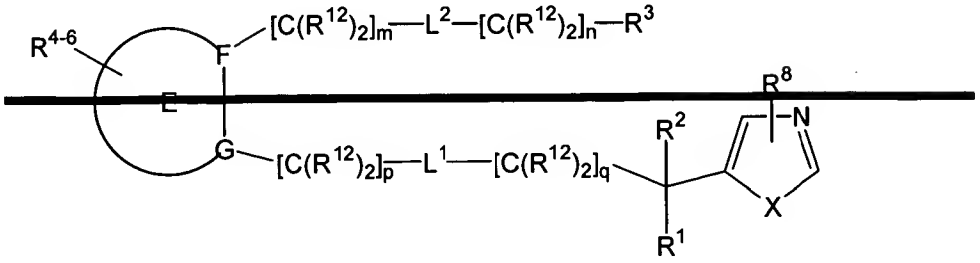
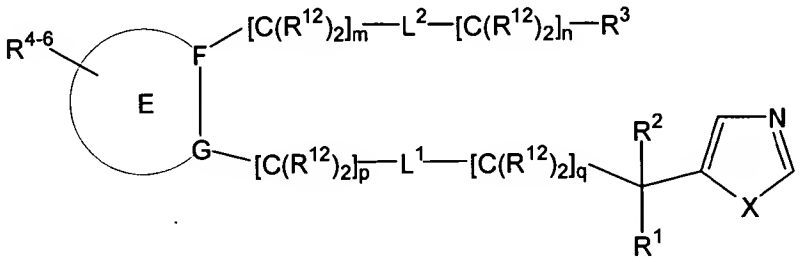
Amendments to the Claims

1 (Currently Amended). A compound of formula (I)





(I),

or a therapeutically acceptable salt thereof, wherein

E is a six-membered aromatic carbocyclic ring in which F and G are C;

L^1 is O;

L^2 is selected from the group consisting of a bond, C_2 alkenylene, C_2 alkynylene, O, NR^9, C(O), S, S(O), SO_2, SO_2NR^9, NR^9SO_2, $C(O)NR^9$, $NR^9C(O)$, and CO_2;

X is NR^7;

R^1 is selected from the group consisting of aryl, arylalkyl, heterocycle, and (heterocycle)alkyl;

R^2 is selected from the group consisting of hydrogen, alkoxy, alkyl, amino, aminoalkyl, cyano, cyanoalkyl, cycloalkyl, cycloalkylalkyl, halo, haloalkyl, heterocycle, (heterocycle)alkyl, hydroxy, and hydroxyalkyl;

R^3 is selected from the group consisting of aryl, heterocycle, and cycloalkyl;

R^{4-6} are each independently selected from the group consisting of hydrogen, $NR^9C(O)$, $C(O)NR^9$, alkanoyl, alkenyl, alkoxy, alkoxyalkyl, alkyl, alkylsulfonyl, alkynyl, amido, amino, aminoalkyl, aminosulfonyl, aryl, arylalkyl, aryloxy, arylsulfonyl, azido, carboxy, cyano, cyanoalkyl, cycloalkyl, cycloalkylalkyl, halo, haloalkoxy, haloalkyl, heterocycle, (heterocycle)alkyl, hydroxy, hydroxyalkyl, nitro, nitroalkyl, oxo, and thio(oxo);

R^7 is selected from the group consisting of hydrogen, alkyl, aryl, cycloalkyl, cycloalkylalkyl, heterocycle, (heterocycle)alkyl, and trialkylsilyl;

R^9 is selected from the group consisting of hydrogen, alkoxyalkyl, alkyl, amidoalkyl, aminoalkyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, carboxyalkyl, heterocycle, (heterocycle)alkyl, hydroxyalkyl, and a nitrogen protecting group;

each R^{12} is independently selected from the group consisting of hydrogen, alkoxy, alkyl, amino, halo, and hydroxy;

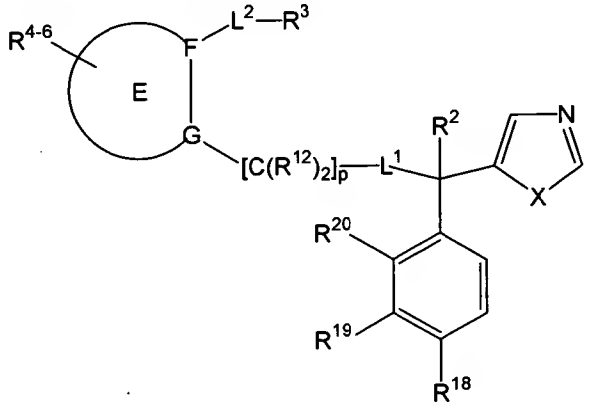
m is 0, 1, 2, 3 or 4;

n is 0, 1, 2, 3 or 4;

p is 0, 1, 2, 3 or 4; and

q is 0, 1, 2, 3 or 4.

2 (Original). A compound according to Claim 1 of formula (II)



(II),

or a therapeutically acceptable salt thereof, wherein

E, F, G, L^1, L^2, X, R^2, R^3, R^{4-6}, R^{12}, and p are as defined in Claim 1 and

R^{18}, R^{19}, and R^{20} are each independently selected from the group consisting of hydrogen, cyano, and halo.

3 (Previously Amended). A compound according to Claim 2 wherein

L^2 is selected from the group consisting of a bond, NR^9SO_2, and $C(O)NR^9$;

wherein each group is drawn with its left end attached to F and its right end attached to R^3;

R^2 is selected from the group consisting of hydrogen and hydroxy;

R^3 is selected from the group consisting of aryl and heterocycle;

R^{12} is hydrogen; and

p is 0 or 1.

18 (Previously Amended). A compound according to Claim 3 wherein one of R^{4-6} is cyano.

19 (Original). A compound according to Claim 18 wherein
R^{18} is cyano; and
R^{19} and R^{20} are hydrogen.

20 (Original). A compound according to Claim 19 selected from the group consisting of 6-(((4-cyanophenyl)(1-methyl-1H-imidazol-5-yl)methoxy)methyl)-3'-methoxy(1,1'-biphenyl)-3-carbonitrile;
6-(((4-cyanophenyl)(1-methyl-1H-imidazol-5-yl)methoxy)methyl)-3'-ethoxy(1,1'-biphenyl)-3-carbonitrile;
3-(1,3-benzodioxol-5-yl)-4-(((4-cyanophenyl)(1-methyl-1H-imidazol-5-yl)methoxy)methyl)benzonitrile;
3'-chloro-6-(((4-cyanophenyl)(1-methyl-1H-imidazol-5-yl)methoxy)methyl)(1,1'-biphenyl)-3-carbonitrile;
N-(5-cyano-2-(((4-cyanophenyl)(1-methyl-1H-imidazol-5-yl)methoxy)methyl)phenyl)-2-thiophenesulfonamide;
N-(5-cyano-2-(((4-cyanophenyl)(1-methyl-1H-imidazol-5-yl)methoxy)methyl)phenyl)-4-methylbenzenesulfonamide;
5-cyano-2-(((4-cyanophenyl)(1-methyl-1H-imidazol-5-yl)methoxy)methyl)-N-(4-methylpyridin-2-yl)benzamide;
N-(3-chlorophenyl)-5-cyano-2-(((4-cyanophenyl)(1-methyl-1H-imidazol-5-yl)methoxy)methyl)benzamide;
4-(((4-cyanophenyl)(1-methyl-1H-imidazol-5-yl)methoxy)methyl)-3-(6-oxo-1-propyl-1,6-dihydropyridin-3-yl)benzonitrile; and
4-(((4-cyanophenyl)(1-methyl-1H-imidazol-5-yl)methoxy)methyl)-3-(6-propoxypyridin-3-yl)benzonitrile.

21 (Previously Amended). A compound according to Claim 3 wherein one of R^{4-6} is halo.

22 (Original). A compound according to Claim 21 wherein R^3 is heterocycle.

23 (Original). A compound according to Claim 22 wherein
R^{18} is cyano; and
R^{19} and R^{20} are hydrogen.

24 (Original). A compound according to Claim 23 selected from the group consisting of 4-(((2-(1,3-benzodioxol-5-yl)-4-chlorobenzyl)oxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile; and4-(((4-chloro-2-(5-formyl-2-thienyl)benzyl)oxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile.

25 (Original). A compound according to Claim 21 wherein R^3 is aryl.

26 (Original). A compound according to Claim 25 wherein the aryl is unsubstituted or substituted with one substituent selected from the group consisting of alkanoyl, alkoxy, alkyl, amino, cyano, formyl, halo, and haloalkyl.

27 (Original). A compound according to Claim 26 wherein
R^{18} is cyano; and
R^{19} and R^{20} are hydrogen.

28 (Previously Amended). A compound according to Claim 27 selected from the group consisting of
4-(((2',5-dichloro(1,1'-biphenyl)-2-yl)methoxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile;
4-(((5-chloro-2'-methyl(1,1'-biphenyl)-2-yl)methoxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile;
4-(((5-chloro-2'-methoxy(1,1'-biphenyl)-2-yl)methoxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile;
4-(((3',5-dichloro(1,1'-biphenyl)-2-yl)methoxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile;
4-(((5-chloro-3'-methyl(1,1'-biphenyl)-2-yl)methoxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile;
4-(((5-chloro-3'-(trifluoromethyl)(1,1'-biphenyl)-2-yl)methoxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile;
4-(((5-chloro-3'-methoxy(1,1'-biphenyl)-2-yl)methoxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile;
4-(((5-chloro-3'-fluoro(1,1'-biphenyl)-2-yl)methoxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile;
4-(((4',5-dichloro(1,1'-biphenyl)-2-yl)methoxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile;

4-(((4-chloro-2-(1-naphthyl)benzyl)oxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile;

4-(((3'-amino-5-chloro(1,1'-biphenyl)-2-yl)methoxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile;

3'-chloro-6'-(((4-cyanophenyl)(1-methyl-1H-imidazol-5-yl)methoxy)methyl)(1,1'-biphenyl)-3-carbonitrile;

4-(((2'-acetyl-5-chloro(1,1'-biphenyl)-2-yl)methoxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile;

4-(((4'-acetyl-5-chloro(1,1'-biphenyl)-2-yl)methoxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile;

4-(((4'-tert-butyl-5-chloro(1,1'-biphenyl)-2-yl)methoxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile;

4-(((5-chloro-3'-ethoxy(1,1'-biphenyl)-2-yl)methoxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile;

N-(5'-chloro-2'-(((4-cyanophenyl)(1-methyl-1H-imidazol-5-yl)methoxy)methyl)(1,1'-biphenyl)-3-yl)acetamide;

4-(((5-chloro-4'-(trifluoromethyl)(1,1'-biphenyl)-2-yl)methoxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile; and

4-(((5-chloro-3'-formyl(1,1'-biphenyl)-2-yl)methoxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile.

29 (Original). A compound according to Claim 25 wherein the aryl is substituted with two or three substituents independently selected from the group consisting of alkoxy, alkyl, and halo.

30 (Original). A compound according to Claim 29 wherein

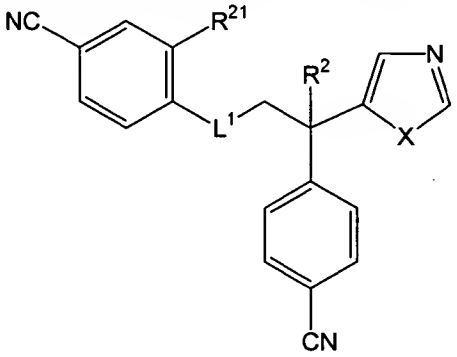
R^{18} is cyano; and

R^{19} and R^{20} are hydrogen.

31 (Original). A compound according to Claim 30 selected from the group consisting of
4-(((5-chloro-3',4'-dimethyl(1,1'-biphenyl)-2-yl)methoxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile;
4-(((5-chloro-2',5'-dimethoxy(1,1'-biphenyl)-2-yl)methoxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile;
4-(((5-chloro-3',4'-dimethoxy(1,1'-biphenyl)-2-yl)methoxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile;

4-(((5-chloro-3',4',5'-trimethoxy(1,1'-biphenyl)-2-yl)methoxy)(1-methyl-1H-imidazol-5-yl)methyl)benzonitrile;
4-((1-methyl-1H-imidazol-5-yl)((2',3',5-trichloro(1,1'-biphenyl)-2-yl)methoxy)methyl)benzonitrile;
4-((1-methyl-1H-imidazol-5-yl)((3',5,5'-trichloro(1,1'-biphenyl)-2-yl)methoxy)methyl)benzonitrile; and
4-((1-methyl-1H-imidazol-5-yl)((3',4',5-trichloro(1,1'-biphenyl)-2-yl)methoxy)methyl)benzonitrile.

32 (Original). A compound according to Claim 1 of formula (III)



(III),

or a therapeutically acceptable salt thereof, wherein
L^1, X, and R^2 are as defined in Claim 1; and
R^{21} is selected from the group consisting of aryl and heterocycle.

33 (Previously Amended). A compound according to Claim 32 wherein
L^1 is O;
X is NR^7; and
R^2 is selected from the group consisting of amino, halo and hydroxy.

38 (Previously Amended). A compound according to Claim 33 wherein
R^2 is hydroxy; and
R^{21} is aryl.

39 (Original). A compound according to Claim 38 selected from the group consisting of 6-(2-(4-cyanophenyl)-2-hydroxy-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-3'-methoxy-1,1'-biphenyl-3-carbonitrile;

6-(2-(4-cyanophenyl)-2-hydroxy-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-3',4'-difluoro-1,1'-biphenyl-3-carbonitrile;
6-(2-(4-cyanophenyl)-2-hydroxy-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-4'-(trifluoromethoxy)-1,1'-biphenyl-3-carbonitrile;
3'-chloro-6-(2-(4-cyanophenyl)-2-hydroxy-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-4'-fluoro-1,1'-biphenyl-3-carbonitrile;
6-(2-(4-cyanophenyl)-2-hydroxy-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-3',5'-difluoro-1,1'-biphenyl-3-carbonitrile;
6-(2-(4-cyanophenyl)-2-hydroxy-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-3'-(trifluoromethoxy)-1,1'-biphenyl-3-carbonitrile;
3',4'-dichloro-6-(2-(4-cyanophenyl)-2-hydroxy-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-1,1'-biphenyl-3-carbonitrile;
3',5'-dichloro-6-(2-(4-cyanophenyl)-2-hydroxy-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-1,1'-biphenyl-3-carbonitrile;
6-(2-(4-cyanophenyl)-2-hydroxy-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-3'-fluoro-1,1'-biphenyl-3-carbonitrile;
3'-chloro-6-(2-(4-cyanophenyl)-2-hydroxy-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-1,1'-biphenyl-3-carbonitrile;
4-(2-(4-cyanophenyl)-2-hydroxy-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-3-(1-naphthyl)benzonitrile; and
(S)-6-(2-(4-cyanophenyl)-2-hydroxy-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-4'-(trifluoromethoxy)-1,1'-biphenyl-3-carbonitrile.

40 (Previously Amended). A compound according to Claim 33 wherein
R^2 is hydroxy; and
R^{21} is heterocycle.

41 (Original). A compound according to Claim 40 selected from the group consisting of
3-(1,3-benzodioxol-5-yl)-4-(2-(4-cyanophenyl)-2-hydroxy-2-(1-methyl-1H-imidazol-5-yl)ethoxy)benzonitrile;
4-(2-(4-cyanophenyl)-2-hydroxy-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-3-quinolin-8-ylbenzonitrile; and
4-(2-(4-cyanophenyl)-2-hydroxy-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-3-(2,2-difluoro-1,3-benzodioxol-5-yl)benzonitrile.

42 (Previously Amended). A compound according to Claim 33 herein

R^2 is halo; and
R^{21} is aryl.

43 (Original). A compound according to Claim 42 selected from the group consisting of
6-(2-(4-cyanophenyl)-2-fluoro-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-3'-methoxy-1,1'-biphenyl-3-carbonitrile;
6-(2-(4-cyanophenyl)-2-fluoro-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-3',4'-difluoro-1,1'-biphenyl-3-carbonitrile;
6-(2-(4-cyanophenyl)-2-fluoro-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-4'-(trifluoromethoxy)-1,1'-biphenyl-3-carbonitrile;
3'-chloro-6-(2-(4-cyanophenyl)-2-fluoro-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-4'-fluoro-1,1'-biphenyl-3-carbonitrile;
6-(2-(4-cyanophenyl)-2-fluoro-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-3',5'-difluoro-1,1'-biphenyl-3-carbonitrile;
6-(2-(4-cyanophenyl)-2-fluoro-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-3'-(trifluoromethoxy)-1,1'-biphenyl-3-carbonitrile;
3',4'-dichloro-6-(2-(4-cyanophenyl)-2-fluoro-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-1,1'-biphenyl-3-carbonitrile;
3',5'-dichloro-6-(2-(4-cyanophenyl)-2-fluoro-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-1,1'-biphenyl-3-carbonitrile;
6-(2-(4-cyanophenyl)-2-fluoro-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-3'-fluoro-1,1'-biphenyl-3-carbonitrile; and
3'-chloro-6-(2-(4-cyanophenyl)-2-fluoro-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-1,1'-biphenyl-3-carbonitrile.

44 (Previously Amended). A compound according to Claim 33 wherein
R^2 is halo; and
R^{21} is heterocycle.

45 (Original). A compound according to Claim 44 selected from the group consisting of
3-(1,3-benzodioxol-5-yl)-4-(2-(4-cyanophenyl)-2-fluoro-2-(1-methyl-1H-imidazol-5-yl)ethoxy)benzonitrile;
4-(2-(4-cyanophenyl)-2-fluoro-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-3-quinolin-8-ylbenzonitrile; and
4-(2-(4-cyanophenyl)-2-fluoro-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-3-(2,2-difluoro-1,3-benzodioxol-5-yl)benzonitrile.

46 (Previously Amended). A compound according to Claim 33 wherein
R^2 is amino; and
R^{21} is aryl.

47 (Original). A compound according to Claim 46 which is 6-(2-amino-2-(4-cyanophenyl)-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-4'-(trifluoromethoxy)-1,1'-biphenyl-3-carbonitrile.

48 (Original). A compound which is 6-(2-(4-cyanophenyl)-2-hydroxy-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-4'-(trifluoromethoxy)-1,1'-biphenyl-3-carbonitrile.

49 (Original). A compound which is 6-((2S)-2-(4-cyanophenyl)-2-hydroxy-2-(1-methyl-1H-imidazol-5-yl)ethoxy)-4'-(trifluoromethoxy)-1,1'-biphenyl-3-carbonitrile.

50 (Original). A pharmaceutical composition comprising a compound of Claim 1 or a therapeutically acceptable salt thereof, in combination with a therapeutically acceptable carrier.

51 (Original). A method for inhibiting farnesyltransferase in a patient in recognized need of such treatment comprising administering to the patient a therapeutically acceptable amount of a compound of Claim 1, or a therapeutically acceptable salt thereof.

52 (Previously Amended). A method for treating cancer by inhibiting farnesyltransferase in a patient in recognized need of such treatment comprising administering to the patient a therapeutically acceptable amount of a compound of Claim 1, or a therapeutically acceptable salt thereof.

Rejections Under 35 U.S.C. 112

Claims 1, 3, 22, and 32 stand rejected under 35 U.S.C. 112, first paragraph, as the Examiner maintains that the specification is not enabling for claiming all heterocycles. Specifically, the Examiner states Applicants have not shown that any and all heterocyclic groups have the same properties.

Applicants traverse the rejection and respectfully request withdrawal of the same.

The Examiner has cited two compounds, from WO01/087845 and US 6,444,687, that do not fit within the claimed genus to show that compounds with different heterocyclic rings in different positions function in different ways and have different binding affinities. The Examiner further states a "thiophene is not equivalent to a pyrididine or a quinoline." Applicants agree that not all heterocycles are "equivalent," however; Applicants respectfully disagree with the Examiner's logic that follows.

It is not surprising the compounds cited by the Examiner have claimed functions other than inhibiting farnesyltransferase, as the cited compounds do not fit within the genus of the instant application. The instant application defines a genus encompassing compounds with a common core that inhibit farnesyltransferase. Applicants have not claimed the compounds the Examiner cited inhibit farnesyltransferase.

Applicants again desire to highlight the support for the breath of their genus claim. The application discloses schemes in conjunction with working examples that support claiming heterocycles generically. (See examples 29, 46 for thiophene; examples 23, 33, 55, 56, 79, 80, 89 for benzene dioxo; examples 59, 60 for quinoline; examples 87 and 92 for pyridine; and example 91 for dihydropyridine). In each of these examples the desired heterocycle is added to the core compound when it is coupled with the corresponding boronic acid in the presence of catalytic palladium and base.

Applicants point to MPEP 2164.02: "The specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation." Applicants maintain that the chemistry required to make heterocyclic compounds of Formula I is consistent with the chemistry in the schemes (see especially Scheme 1) and examples and leaves no undue experimentation for one skilled in the art.

The Examiner has also objected to the specification because "it does not provide any data that these compounds do treat cancer." Applicants respectfully traverse this objection and request withdrawal of the same.

On pages 15-16 of the specification, Tables 1 and 2, the Applicants have provided biological activity data for 93 compounds. The data shows % inhibition of farnesyltransferase. It is well known that farnesyltransferase plays a pivotal role in tumor formation (see page 1 of

the specification and all references cited in lines 26-28 of page 1). "...if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the Examiner has evidence that the model does not correlate" (MPEP 2164.02). Hence, since it is well known in the art that inhibiting farnesyltransferase reduces tumor formation, and since the Examiner has provided no evidence that the inhibition of farnesyltransferase and the reduction of tumor formation do not correlate, this objection cannot stand.

Rejections Under 35 U.S.C. 101

Claim 51 stands rejected for lacking utility. Applicants traverse the rejection and respectfully request withdrawal of the same. Applicants have demonstrated the inventive compounds are potent inhibitors of farnesyltransferase. As stated above, it is well known that inhibiting farnesyltransferase slows tumor formation and metastasis. Therefore, Applicants maintain there is inherent utility in inhibiting farnesyltransferase and this utility is recognized by all those skilled in the art.

Rejections Under 35 U.S.C. 112

Claim 1 stands rejected under 35 U.S.C. 112 for reciting R^8 without antecedent basis. Claim 1 has been amended to remove R^8. This rejection is thus rendered moot.

Claims 28 and 31 stand rejected under 35 U.S.C. 112. The Examiner maintains there is no recitation of the cyano group in the species claimed. Applicants traverse this rejection and request withdrawal of the same. Each of the claimed compounds do have the cyano limitation. Applicants respectively point out that "benzonitrile" is a benzene ring with a cyano substitution.

Claims 27 and 31 stand rejected under 35 U.S.C. 112. The Examiner maintains there is no recitation of the cyano group in the species. Applicants traverse and request withdrawal of the same. Again, Applicants respectively point out that "benzonitrile" is a benzene ring with a cyano substitution.

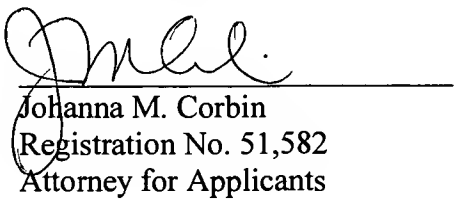
Rejections Under 35 U.S.C. 102

Claim 1 stands rejected under 35 U.S.C. 102(b) as being anticipated by US 5030644 Balwin et al. and Brain Philips et al. Applicants respectfully traverse this rejection and request withdrawal of the same. The amendment to Claim 1 renders both rejections under 35 U.S.C. 102(b) moot.

ACTION REQUESTED

For all the forgoing reasons, Applicants submit that Claims 1-3, 18-33, and 38-52 are in condition for allowance. To that end, the examiner is invited to contact the undersigned to schedule an Examiner Interview to discuss any matter.

Respectfully submitted,
Claiborne, *et al.*



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